General

Guideline Title

Dyspepsia and gastro-oesophageal reflux disease. Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Dyspepsia and gastro-oesophageal reflux disease. Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 43 p. (Clinical guideline; no. 184).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version:

National Institute for Clinical Excellence (NICE). Dyspepsia: management of dyspepsia in adults in primary care. 2005 addendum. London (UK): National Institute for Clinical Excellence (NICE); 2005 Jun. 47 p. (Clinical guideline; no. 17).

North of England Dyspepsia Guideline Development Group. Dyspepsia: managing dyspepsia in adults in primary care. Newcastle upon Tyne (UK): Centre for Health Services Research, University of Newcastle; 2004 Aug. 228 p. [466 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone Antibacterial Drugs : The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Institute for Health and Care Excellence (NICE) Internal Guidelines Development Program. See the "Availability of Companion Documents" field for the full version of this guidance.

Recommendations are marked as [new 2014], [2014], [2004] or [2004, amended 2014]:

- [new 2014] indicates that the evidence has been reviewed and the recommendation has been added or updated
- [2014] indicates that the evidence has been reviewed but no change has been made to the recommended action
- [2004] indicates that the evidence has not been reviewed since 2004
- [2004, amended 2014] indicates that the evidence has not been reviewed since 2004, but changes have been made to the recommendation wording that change the meaning.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

The Community Pharmacist

Community pharmacists should offer initial and ongoing help for people with symptoms of dyspepsia. This includes advice about lifestyle changes, using over-the-counter medication, help with prescribed drugs and advice about when to consult a general practitioner (GP). [2004]

Community pharmacists should record adverse reactions to treatment and may participate in primary care medication review clinics. [2004]

Common Elements of Care

Offer simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation. [2004]

Advise people to avoid known precipitants they associate with their dyspepsia where possible. These include smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Raising the head of the bed and having a main meal well before going to bed may help some people. [2004]

Provide people with access to educational materials to support the care they receive. [2004]

Recognise that psychological therapies, such as cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people. [2004, amended 2014]

Encourage people who need long-term management of dyspepsia symptoms to reduce their use of prescribed medication stepwise: by using the effective lowest dose, by trying 'as-needed' use when appropriate, and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or comedication that needs continuing treatment). [2004, amended 2014]

Referral Guidance for Endoscopy

For people presenting with dyspepsia together with significant acute gastrointestinal bleeding, refer them immediately (on the same day) to a specialist. [2004] (see also the NGC summary of the NICE guideline Acute upper gastrointestinal bleeding: management [NICE clinical guideline 141].)

Review medications for possible causes of dyspepsia (for example, calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids and non-steroidal anti-inflammatory drugs [NSAIDs]). In people needing referral, suspend NSAID use. [2004]

Think about the possibility of cardiac or biliary disease as part of the differential diagnosis. [2004, amended 2014]

If people have had a previous endoscopy and do not have any new alarm signs* consider continuing management according to previous endoscopic findings. [2004]

*For more information about alarm signs see the NICE guideline Referral for suspected cancer ([NICE clinical guideline 27] [update in progress; publication expected May 2015. For more information see http://guidance.nice.org.uk/CG/Wave0/618]).

Interventions for Uninvestigated Dyspepsia

Be aware that dyspepsia in unselected people in primary care is defined broadly to include people with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting. Also see the recommendations under "Common Elements of Care" above. [2004, amended 2014]

Leave a 2-week washout period after proton pump inhibitor (PPI) use before testing for *Helicobacter pylori* (hereafter referred to as *H pylori*) with a breath test or a stool antigen test. [2004, amended 2014]

Offer empirical full-dose PPI therapy (see Table 1 in Appendix A in the original guideline document) for 4 weeks to people with dyspepsia. [2004]

Offer *H pylori* 'test and treat' to people with dyspepsia. [2004]

If symptoms return after initial care strategies, step down PPI therapy to the lowest dose needed to control symptoms. Discuss using the treatment on an 'as-needed' basis with people to manage their own symptoms. [2004]

Offer H_2 receptor antagonist (H_2RA) therapy if there is an inadequate response to a PPI. [2004, amended 2014]

Reviewing Patient Care

Offer people who need long-term management of dyspepsia symptoms an annual review of their condition, and encourage them to try stepping down or stopping treatment (unless there is an underlying condition or comedication that needs continuing treatment). [2004, amended 2014]

Advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the-counter and taken as needed). [2004, amended 2014]

Interventions for Gastro-oesophageal Reflux Disease (GORD)

Manage uninvestigated 'reflux-like' symptoms as uninvestigated dyspepsia. [2004, amended 2014]

Offer people with GORD a full-dose PPI (see Table 1 in Appendix A in the original guideline document) for 4 or 8 weeks. [2004]

If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms. [2004, amended 2014]

Discuss with people how they can manage their own symptoms by using the treatment when they need it. [2004]

Offer H_2RA therapy if there is an inadequate response to a PPI. [2004, amended 2014]

People who have had dilatation of an oesophageal stricture should remain on long-term full-dose PPI therapy (see Table 1 in Appendix A in the original guideline document). [2004]

Offer people a full-dose PPI (see Table 2 in Appendix A in the original guideline document) for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs). [new 2014]

If initial treatment for healing severe oesophagitis fails, consider a high dose of the initial PPI, switching to another full-dose PPI or switching to another high-dose PPI (see Table 2 in Appendix A in the original guideline document), taking into account the person's preference and clinical circumstances (for example, tolerability of the initial PPI, underlying health conditions and possible interactions with other drugs). [new 2014]

Offer a full-dose PPI (see Table 2 in Appendix A in the original guideline document) long-term as maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other drugs), and the acquisition cost of the PPI. [new 2014]

If the person's severe oesophagitis fails to respond to maintenance treatment, carry out a clinical review. Consider switching to another PPI at full dose or high dose (see Table 2 in Appendix A in the original guideline document), taking into account the person's preference and clinical circumstances, and/or seeking specialist advice. [new 2014]

Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (for example, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus hernia, oesophageal stricture or oesophageal ulcers, or male gender). [new 2014]

Interventions for Peptic Ulcer Disease

Offer *H pylori* eradication therapy to people who have tested positive for *H pylori* and who have peptic ulcer disease. Also see "*H pylori* Testing and Eradication," below. [2004]

For people using NSAIDs with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full-dose PPI (see Table 1 in Appendix A in the original guideline document) or H_2RA therapy for 8 weeks and, if *H pylori* is present, subsequently offer eradication therapy. [2004]

Offer people with gastric ulcer and *H pylori* repeat endoscopy 6 to 8 weeks after beginning treatment, depending on the size of the lesion. [2004, amended 2014]

Offer people with peptic ulcer (gastric or duodenal) and *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion. [2004, amended 2014]

Offer full-dose PPI (see Table 1 in Appendix A in the original guideline document) or H_2RA therapy for 4 to 8 weeks to people who have tested negative for *H pylori* who are not taking NSAIDs. [2004]

For people continuing to take NSAIDs after a peptic ulcer has healed, discuss the potential harm from NSAID treatment. Review the need for NSAID use regularly (at least every 6 months) and offer a trial of use on a limited, 'as needed' basis. Consider reducing the dose, substituting an NSAID with paracetamol, or using an alternative analgesic or low-dose ibuprofen (1.2 g daily). [2004]

In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, offer gastric protection or consider substitution with a cyclooxygenase (COX)-2-selective NSAID. [2004]

In people with an unhealed ulcer, exclude non-adherence, malignancy, failure to detect *H pylori*, inadvertent NSAID use, other ulcer-inducing medication and rare causes such as Zollinger–Ellison syndrome or Crohn's disease. [2004]

If symptoms recur after initial treatment, offer a PPI to be taken at the lowest dose possible to control symptoms. Discuss using the treatment on an 'as needed' basis with people to manage their own symptoms. [2004, amended 2014]

Offer H_2RA therapy if there is an inadequate response to a PPI. [2004]

Interventions for Functional Dyspepsia

Manage endoscopically determined functional dyspepsia using initial treatment for *H pylori* if present, followed by symptomatic management and periodic monitoring. [2004]

Offer eradication therapy to people testing positive for *H pylori*. [2004]

Do not routinely offer retesting after eradication, although the information it provides may be valued by individual people. [2004]

If *H pylori* has been excluded and symptoms persist, offer either a low-dose PPI (see Table 1 in Appendix A in the original guideline document) or an H_2RA for 4 weeks. [2004, amended 2014]

If symptoms continue or recur after initial treatment, offer a PPI or H_2RA to be taken at the lowest dose possible to control symptoms. [2004, amended 2014]

Discuss using PPI treatment on an 'as-needed' basis with people to manage their own symptoms. [2004]

Avoid long-term, frequent dose, continuous antacid therapy (it only relieves symptoms in the short term rather than preventing them). [2004, amended 2014]

Helicobacter Pylori Testing and Eradication

Testing

Test for *H pylori* using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology where its performance has been locally validated. [2004, amended 2014]

Perform retesting for *H pylori* using a carbon-13 urea breath test. (There is currently insufficient evidence to recommend the stool antigen test as a test of eradication†.) [2004]

Do not use office-based serological tests for *H pylori* because of their inadequate performance. [2004, amended 2014]

†This refers to evidence reviewed in 2004.

Eradication

First-Line Treatment

Offer people who test positive for *H pylori* a 7-day, twice-daily course of treatment with:

- A PPI (see Table 3 in Appendix A in the original guideline document) and
- Amoxicillin and
- Either clarithromycin or metronidazole

Choose the treatment regimen with the lowest acquisition cost, and take into account previous exposure to clarithromycin or metronidazole. [new 2014]

Offer people who are allergic to penicillin‡ a 7-day, twice-daily course of treatment with:

- A PPI (see Table 3 in Appendix A in the original guideline document) and
- Clarithromycin and
- Metronidazole [new 2014]

Offer people who are allergic to penicillin‡ and who have had previous exposure to clarithromycin a 7-day, twice-daily course of treatment with:

- A PPI (see Table 3 in Appendix A in the original guideline document) and
- Bismuth and
- Metronidazole and
- Tetracycline [new 2014]

Discuss treatment adherence with the person and emphasise its importance. For more information about supporting adherence, see the NICE guideline Medicines adherence. Involving patients in decisions about prescribed medicines and supporting adherence (NICE clinical guideline 76). [new 2014]

Second-Line Treatment

Offer people who still have symptoms after first-line eradication treatment a 7-day, twice-daily course of treatment with:

- A PPI (see Table 3 in Appendix A in the original guideline document) and
- Amoxicillin and
- Either clarithromycin or metronidazole (whichever was not used first-line) [new 2014]

Offer people who have had previous exposure to clarithromycin and metronidazole a 7-day, twice-daily course of treatment with:

- A PPI (see Table 3 in Appendix A in the original guideline document) and
- Amoxicillin and
- A quinolone or tetracycline (whichever has the lowest acquisition cost) [new 2014]

Offer people who are allergic to penicillin[c] (and who have not had previous exposure to a quinolone) a 7-day, twice-daily course of treatment with:

- A PPI (see Table 3 in Appendix A in the original guideline document) and
- Metronidazole and
- Levofloxacin [new 2014]

Offer people who are allergic to penicillin‡ and who have had previous exposure to a quinolone:

- A PPI (see Table 3 in Appendix A in the original guideline document) and
- Bismuth and
- Metronidazole and
- Tetracycline [new 2014]

Seek advice from a gastroenterologist if eradication of *H pylori* is not successful with second-line treatment. [new 2014]

‡For the assessment of allergy to beta-lactam antibiotics and referral to specialist care, please see the NICE guideline Drug allergy: diagnosis and management of drug allergy in adults, children and young people (NICE clinical guideline 183).

Laparoscopic Fundoplication

Consider laparoscopic fundoplication for people who have:

- A confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy, but who do not wish to continue with this therapy long term
- A confirmed diagnosis of acid reflux and symptoms that are responding to a PPI, but who cannot tolerate acid suppression therapy [new 2014]

Referral to a Specialist Service

Consider referral to a specialist service for people:

- Of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained¶
- With suspected GORD who are thinking about surgery
- With *H pylori* that has not responded to second-line eradication therapy. [new 2014]

¶In the NICE Referral guidelines for suspected cancer (NICE clinical guideline 27), 'unexplained' is defined as 'a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any)'. (Please note that an update is in progress; publication expected May 2015. For more information see http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618.)

Surveillance for People with Barrett's Oesophagus

Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:

- The presence of dysplasia (see the NICE guideline Barrett's oesophagus – ablative therapy for the treatment of Barrett's oesophagus [NICE clinical guideline 106])
- The person's individual preference
- The person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment)

Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer (for example, people with stable non-dysplastic Barrett's oesophagus). [new 2014]

Definitions:

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendation Wording in Guideline Updates

The National Institute for Health and Care Excellence (NICE) began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2004] (see above for details about how recommendations are labelled). In particular, for recommendations labelled

[2004] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Clinical Algorithm(s)

The following algorithms are provided in the full version of the original guideline document (see the "Availability of Companion Documents" field):

- Flowchart to guide pharmacist management of dyspepsia
- Flowchart of referral criteria and subsequent management
- Flowchart for the interventions for uninvestigated dyspepsia
- Flowchart for interventions for GORD
- Flowchart for duodenal ulcer
- Flowchart for gastric ulcer
- Flowchart for functional dyspepsia

A National Institute for Health and Care Excellence (NICE) pathway titled "Dyspepsia and Gastro-oesophageal Reflux Disease Overview" is available on the NICE Web site .

Note: The flowcharts included within the full version of the guideline are intended as an aide memoire to promote the effective care for managing people with dyspepsia. Within the flowcharts the boxes shaded in orange reflect the recommendations that are new or amended in 2014. The grey boxes and corresponding footnotes in the flowcharts are information or recommendations from 2004 no longer included in this guideline. The white boxes represent information or recommendations from 2004 that have not been altered.

Scope

Disease/Condition(s)

- Dyspepsia
- Gastro-oesophageal reflux disease (GORD)
- Peptic ulcer disease
- Barrett's oesophagus

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Surgery

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To offer best practice advice on the care of adults (18 years and older) with symptoms of dyspepsia or symptoms suggestive of gastro-oesophageal reflux disease (GORD), or both

Target Population

- Adults with symptoms of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease (GORD), or both
- Adults with a diagnosis of Barrett's oesophagus who are undergoing endoscopic surveillance

Note: This guideline update does not include children and young people (younger than 18 years) and people with a diagnosis of oesophagogastric cancer.

Interventions and Practices Considered

1. Role of the community pharmacist in assisting people with symptoms of dyspepsia
2. Common elements of care
    - Offering lifestyle advice (healthy eating, weight reduction, smoking cessation)
    - Avoiding known precipitants of dyspepsia
    - Providing education materials
    - Psychological therapies
    - Stepwise reduction in prescribed medications
3. Referral for endoscopy
    - Urgent referral of acute gastrointestinal bleeding
    - Review of medications for possible cause of dyspepsia
4. Interventions for uninvestigated dyspepsia
    - Empirical proton-pump inhibitor (PPI) therapy for dyspepsia
    - *Helicobacter pylori* testing with a breath test or stool antigen test
    - H_2 receptor antagonist (H_2RA) therapy if inadequate response to a PPI
5. Reviewing patient care during long-term management of dyspepsia
6. Interventions for gastro-oesophageal reflux disease (GORD)
    - PPI therapy
    - H_2RA therapy
    - Endoscopy
7. Interventions for peptic ulcer disease
    - *H pylori* eradication therapy
    - PPI therapy
    - *H pylori* retesting
    - Endoscopy
    - Review of non-steroidal anti-inflammatory drugs (NSAIDs)
    - Cyclooxygenase-2 (COX-2)-selective NSAIDs
8. Interventions for functional dyspepsia

    - *H pylori* eradication therapy
    - PPI or H_2RA therapy
    - Avoiding long-term antacid therapy
9. *H pylori* testing and eradication
    - Carbon-13 urea breath test or a stool antigen test, or laboratory-based serology
    - Retesting for *H pylori* using a carbon-13 urea breath test
    - First-line eradication therapy: PPI + amoxicillin + clarithromycin or metronidazole
    - Alternative eradication therapies for penicillin-allergic individuals
    - Second-line eradication therapies
10. Laparoscopic fundoplication
11. Referral to a specialist service
12. Surveillance for people with Barrett's oesophagus

Major Outcomes Considered

- Reduction in symptoms (severity/frequency)
- Biopsy findings (pathology)
- Endoscopic appearance of oesophagus
- Health-related quality of life (measured using EQ-5D and/or disease-specific tools)
- Reduction in medication requirement (frequency and dose)
- Adverse effects of interventions (diagnostic or treatment)
- Resource use and costs
- Occurrence of Barrett's oesophagus and progression to adenocarcinoma

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Institute for Health and Care Excellence (NICE) Internal Guidelines Development Program. See the "Availability of Companion Documents" field for the full version of this guidance.

Full systematic reviews of each review questions for the update strictly followed the review protocols (see Appendix C in the full version of the original guideline document [see the Availability of Companion Documents" field]) as set out based on the Guideline Manual 2012, and agreed by the Guideline Development Group (GDG).

Scoping Searches

Scoping searches were undertaken in September 2011 to provide information for scope development project planning. Browsing or simple search strategies were employed. See Appendix C (section C.2) for a list of the databases and websites searched.

Main Searches

Sources searched for the guideline:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)

- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Identification of Evidence for Clinical Questions

The searches were conducted between November 2011 and May 2013. The aim of the searches was to identify evidence for each of the clinical questions being asked. The MEDLINE search strategies and specific inclusion/exclusion criteria for each question are presented in Appendix C in the full version of the original guideline document. The MEDLINE search strategies were translated for use in all of the other databases. Updated searches were also conducted in December 2013.

Economic Evaluations and Quality of Life Data

Sources Searched to Identify Economic Evaluations

- National Health Service Economic Evaluation Database – NHS EED (Wiley)
- Health Economic Evaluations Database – HEED (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The specific economic evaluations filter was appended to the search strategy to identify relevant evidence. See Appendix C in the full version of the original guideline document for the specific search strategies used and dates for the various economic topics.

Number of Source Documents

The number of studies identified for each clinical question is provided in the full version of the original guideline document (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Institute for Health and Care Excellence (NICE) Internal Guidelines Development Program. See the "Availability of Companion Documents" field for the full version of this guidance.

Full systematic reviews of each review questions for the update strictly followed the review protocols (see Appendix C of the full version of the guideline document) as set out based on the Guideline Manual 2012, and agreed by the Guideline Development Group (GDG). Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for appraising the quality of the evidence where appropriate, and the Linking Evidence to Recommendations (LETR) framework was adopted to transparently document the GDG's decision-making process. Further information on the modified GRADE approach and network meta-analysis is documented in Appendix C, Section C3 and Appendix E in the full version of the original guideline document.

Summary of the Modified GRADE Approach

For the review questions:

- Review question 1: When should (and with what indications) patients with uninvestigated dyspepsia be referred for endoscopy for further investigation and review of treatment plan?
- Review question 2: Which risk factors indicate endoscopy in order to exclude Barrett's oesophagus?
- Review question 3: Which patient characteristics/clinical indicators/criteria indicate referral of a patient with dyspepsia, heartburn, or confirmed gastro-oesophageal reflux disease (GORD) managed in primary care to a consultant led medical or surgical service (specialist services)?

For the above three review questions, a modified-GRADE approach was used for critical appraisal and evidence synthesis to aid decision making.

Outcome vs Individual Study, and Meta-analysis

In GRADE approach for intervention question, the quality of evidence on each outcome is assessed according to the impact of the risk of bias from the study to that particular outcome. If there is more than one study that reported such outcome, the overall judgement of the quality for that outcome across different studies will be made. This is because in the same intervention study (e.g., randomised controlled trial [RCT]), there may be different levels or magnitude of the impact of the risk of bias on different outcomes measured in the same study. For example, in a single-blinded RCT (assessor-blinded only) on antibiotics for infected wound, the risk of bias for patient-reported pain of the wound (outcome 1) would be different compared to bacteria eradication rate (based on histology) (outcome 2) due to the single-blinded design of the study.

In a prognostic study (or clinical prediction model), these varying degrees of risk of bias in a study do not apply same as in an intervention study. This is because in a multivariate regression model (MRM), the sources of the risk of bias commonly came from how the data of the individual risk factors or predictors was collected as a whole in a study, and what kinds of adjustment were made in the MRM regarding baseline confounders and covariates. Hence, the risk of bias in a study would have impacted the MRM as whole (i.e., all risk factors or predictors entered in the MRM equally). Therefore, the quality of an individual study would apply across to all risk factors or predictors in that particular individual study.

Due to the varying methods used in different studies (e.g., different multivariate regression models in different studies used different dependent variables as risk factors or predictors, used different covariates, adjusted for different confounding factors), in other words, there are no two exactly identical multivariate regression models that could be pooled in its entirety. The only approach to conduct meta-analysis is to obtain individual participant data (IPD) data from each study and then re-run a single MRM using all the IPD data from all included studies. This would be outside the development timeframe of this guideline.

Therefore, no meta-analysis was conducted to combine individual risk factors or predictors across different MRMs in different studies. Nevertheless, if there are more than one included studies for a particular risk factor or predictor, the evidence would be presented based on individual risk factors or predictors across different studies to aid discussion and decision making. Otherwise, the evidence would be presented as individual studies.

Criteria and Downgrading

There are four quality categories in GRADE, namely 'High', 'Moderate', 'Low' and 'Very low'. For prognostic study (or clinical prediction model), case control or cross-sectional study was considered as appropriate study designs and hence under the modified-GRADE approach, these two study designs would start from 'High' quality (or high 'confidence' in the effect estimates). Then the evidence would be downgraded based on a modified framework.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

The development of this guideline update was managed in accordance with the process and methods outlines in the National Institute for Health and Care Excellence (NICE) Guidelines Manual 2012 (see the "Availability of Companion Documents" field), which are different from the process and methods used to develop CG17 [2004]. This is the case for the evidence presented in chapters 4.2, 4.4, 4.7, 4.8, 4.9, 4.10 and 4.11 in the full version of the original guideline document (see the "Availability of Companion Documents" field). There is more information about how NICE clinical guidelines are currently developed on the NICE website. A booklet, How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS , is available.

Full systematic reviews of each review questions for the update strictly followed the review protocols (see Appendix C of the full version of the guideline document) as set out based on the Guideline Manual 2012, and agreed by the Guideline Development Group (GDG). Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for appraising the quality of the evidence where appropriate, and the Linking Evidence to Recommendations (LETR) framework was adopted to transparently document the GDG's decision-making process. Further information on the modified GRADE approach and network meta-analysis is documented in Appendix C, Section C3 and Appendix E in the full version of the original guideline document.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words are used (for example, 'do not offer…') when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendation Wording in Guideline Updates

The National Institute for Health and Care Excellence (NICE) began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2004] (see the "Major Recommendations" field for details about how recommendations are labelled). In particular, for recommendations labelled [2004] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Cost Analysis

Appendix H in the full version of the original guideline document contains the full health economics report (see the "Availability of Companion Documents" field). The report contains economic models on the following topics:

- Proton pump inhibitors (PPIs) in the healing and maintenance of severe erosive reflux oesophagitis
    - What is the clinical effectiveness of PPIs in patients with severe erosive reflux disease?
        i. To control/reduce oesophagitis
        ii. As maintenance therapy
- Eradication of *Helicobacter pylori*
    i. In patients with symptoms of dyspepsia who are positive for *H pylori*, which eradication regimens are the most clinically effective in the eradication of *H pylori?*
    ii. What *H pylori* eradication regimens should be offered as second-line (or third-line) treatments when first-line treatments fail?

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was validated through two consultations.

1. The first draft of the guideline (the full guideline, National Institute for Health and Care Excellence [NICE] guideline, and Quick Reference Guide) were consulted with Stakeholders and comments were considered by the Guideline Development Group (GDG)
2. The final consultation draft of the Full guideline, the NICE guideline and the Information for the Public were submitted to stakeholders for final comments.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of individuals with dyspepsia and gastro-oesophageal reflux disease (GORD)

Refer to the "Trade off between clinical benefits and harms" sections in the full version of the original guideline document (see the "Availability of Companion Documents" field) for benefits of specific interventions.

Potential Harms

- There is a small but definite risk of harm (perforation and gastrointestinal [GI] bleeding) from the endoscopy procedure.
- Misoprostol is associated with a significant incidence of diarrhoea, nausea and abdominal pain.
- *Helicobacter pylori* eradication regimens are associated with antibiotic resistance and adverse events including loose stools, dermatitis, rash, mouth dryness, oral candidiasis, and abnormal liver function test.
- Low-quality evidence from 3 randomised controlled trials showed that there were significantly more serious adverse events (bleeding,

perforation, pneumothorax, dysphagia) in patients receiving laparoscopic fundoplication than those treated by medical management including a proton pump inhibitor (PPI).
- Adverse effects of PPIs
- There is some concern about the renal and cardiovascular safety of cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs). While reporting a similar reduction in ulceration to celecoxib, the VIGOR trial of rofecoxib reported an excess of cardiovascular deaths. The trial comparing celecoxib with diclofenac and omeprazole found that celecoxib was as likely to cause acute renal failure in patients with pre-existing renal impairment as diclofenac (40%). A recent review of the VIGOR and CLASS trials found that severe non-gastrointestinal adverse events actually increased in patients receiving a COX-2 selective NSAIDs. While COX-2 selective NSAIDs do appear to reduce gastrointestinal harm, severe events are rare and the clinical benefit may be small in any but those at high risk of ulceration.

Refer to the "Trade off between clinical benefits and harms" sections in the full version of the original guideline document (see the "Availability of Companion Documents" field) for harms of specific interventions.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summaries of product characteristics of any drugs.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- Patients and healthcare professionals have rights and responsibilities as set out in the National Health Service (NHS) Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.
- NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.
- This guideline recommends some drugs for indications for which they do not have a United Kingdom (UK) marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.
- For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Care Excellence (NICE) has developed tools and resources to help organizations implement this guidance. These are available on the NICE Web site (see also the "Availability of Companion Documents" field).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Referral Guidance for Endoscopy

For people presenting with dyspepsia together with significant acute gastrointestinal bleeding, refer them immediately (on the same day) to a specialist. [2004] (see the National Guideline Clearinghouse [NGC] summary of the NICE guideline Acute upper gastrointestinal bleeding: management [NICE clinical guideline 141].)

Interventions for Uninvestigated Dyspepsia

Leave a 2-week washout period after proton pump inhibitor (PPI) use before testing for *Helicobacter pylori* (hereafter referred to as *H pylori*) with a breath test or a stool antigen test. [2004, amended 2014]

Interventions for Gastro-oesophageal Reflux Disease (GORD)

Offer people a full-dose PPI (see Table 2 in Appendix A in the original guideline document [see the "Availability of Companion Documents" field]) for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs). [new 2014]

Offer a full-dose PPI (see Table 2 in Appendix A in the original guideline document [see the "Availability of Companion Documents" field]) long-term as maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other drugs), and the acquisition cost of the PPI. [new 2014]

Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (for example, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus hernia, oesophageal stricture or oesophageal ulcers, or male gender). [new 2014]

Interventions for Peptic Ulcer Disease

Offer *H pylori* eradication therapy to people who have tested positive for *H pylori* and who have peptic ulcer disease. Also see the recommendations under *H pylori* testing and eradication. [2004]

For people using non-steroidal anti-inflammatory drugs (NSAIDs) with diagnosed peptic ulcer, stop the use of NSAIDs where possible. Offer full-dose PPI (see Table 1 in Appendix A in the original guideline document) or H_2 receptor antagonist [H_2RA] therapy for 8 weeks and, if *H pylori* is present, subsequently offer eradication therapy. [2004]

Offer people with peptic ulcer (gastric or duodenal) and *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion. [2004, amended 2014]

Referral to a Specialist Service

Consider referral to a specialist service for people:

- Of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained*
- With suspected GORD who are thinking about surgery
- With *H pylori* that has not responded to second-line eradication therapy. [new 2014]

*In the NICE Referral guidelines for suspected cancer (NICE clinical guideline 27), 'unexplained' is defined as 'a symptom(s) and/or sign(s) that has not led to a diagnosis being made by the primary care professional after initial assessment of the history, examination and primary care investigations (if any)'. (Please note that an update is in progress; publication expected May 2015. For more information see http://www.nice.org.uk/Guidance/InDevelopment/GID-CGWAVE0618.)

Surveillance for People with Barrett's Oesophagus

Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:

- The presence of dysplasia (see the NICE guideline Barrett's oesophagus – ablative therapy for the treatment of Barrett's oesophagus [NICE clinical guideline 106])
- The person's individual preference
- The person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).

Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer (for example, people with stable non-dysplastic Barrett's oesophagus). [new 2014]

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Mobile Device Resources

Patient Resources

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Dyspepsia and gastro-oesophageal reflux disease. Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 43 p. (Clinical guideline; no. 184).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

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Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The details of declared interests and the actions taken for Guideline Development Group members are shown in Appendix A in the full version in the original guideline document (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version:

National Institute for Clinical Excellence (NICE). Dyspepsia: management of dyspepsia in adults in primary care. 2005 addendum. London (UK): National Institute for Clinical Excellence (NICE); 2005 Jun. 47 p. (Clinical guideline; no. 17).

North of England Dyspepsia Guideline Development Group. Dyspepsia: managing dyspepsia in adults in primary care. Newcastle upon Tyne (UK): Centre for Health Services Research, University of Newcastle; 2004 Aug. 228 p. [466 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Dyspepsia and gastro-oesophageal reflux disease. Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 322 p. (Clinical guideline; no. 184). Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Dyspepsia and gastro-oesophageal reflux disease. Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both. Appendices. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. (Clinical guideline; no. 184). Available from the NICE Web site .
- Dyspepsia and gastro-oesophageal reflux disease. Costing statement. London (UK): National Institute for Health and Care Excellence; 2014 Sep. 8p. (Clinical guideline; no. 184). Electronic copies: Available from the NICE Web site .
- Dyspepsia and gastro-oesophageal reflux disease - *Helicobacter pylori* testing and eradication. Clinical audit tool. London (UK): National Institute for Health and Care Excellence; 2014 Sep. (Clinical guideline; no. 184). Electronic copies: Available from the NICE Web site .
- Dyspepsia and gastro-oesophageal reflux disease - interventions. Clinical audit tool. London (UK): National Institute for Health and Care Excellence; 2014 Sep. (Clinical guideline; no. 184). Electronic copies: Available from the NICE Web site .
- Dyspepsia and gastro-oesophageal reflux disease. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence; 2014 Sep. (Clinical guideline; no. 184). Electronic copies: Available from the NICE Web site .
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Electronic copies: Available from the NICE Archive Web site .

Patient Resources

The following are available:

- Indigestion, heartburn and reflux in adults. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 16 p. (Clinical guideline; no. 184). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site .
- Dyspepsia/GORD: option grid to help people make decisions about long term heartburn treatment. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Sep. 1 p. (Clinical guideline; no. 184). Electronic copies: Available from the NICE Web site .

NGC Status

This NGC summary was completed by ECRI on January 24, 2005. This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on October 31, 2014. This summary was updated by ECRI Institute on September 21, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on May 18, 2016 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs.

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